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Effects of inotropes on human leucocyte numbers, neutrophil function and lymphocyte subtypes

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Summary

We have investigated the effects of inotropes with different adrenergic receptor specificity on differential white cell count, lymphocyte subtypes and neutrophil function in healthy volunteers. Six healthy, male volunteers were enrolled into this randomized, placebo-controlled pilot study. Each volunteer was studied on four separate occasions during a 2-h infusion of various agents, and for 2 h after stopping the infusion. The agents investigated were adrenaline 0.1 μg kg^{-1} min^{-1}, dobutamine 5 μg kg^{-1} min^{-1}, dopexamine 2 μg kg^{-1} min^{-1} and 5% glucose 0.5 ml kg^{-1} h^{-1}. Venous blood was sampled at 0, 30, 120 and 240 min. Haemodynamic monitoring was continued throughout the study. Full blood count, white cell differential count and enumeration of lymphocyte subtypes were performed. Neutrophil function tests included chemoluminescence, and assessment of neutrophil chemotaxis, phagocytosis and adhesion. The Wilcoxon signed rank test was used to compare differences between placebo and active drugs at each time compared with baseline. There was a significant increase in white cell count, lymphocyte count and neutrophil count with adrenaline, and a small but significant decrease in these variables with dobutamine and dopexamine. These changes were also apparent for absolute CD3$^+$, CD4$^+$ and CD8$^+$ lymphocyte counts. Neutrophil respiratory burst in response to f-methionyl-leucyl-phenylalanine increased significantly only with adrenaline at 30 min ($P=0.046$). There were no other significant changes in tests of neutrophil function. Infusion of inotropes was associated with changes in white cell numbers, lymphocyte subtypes and neutrophil respiratory burst. In healthy volunteers, adrenaline had effects different from those of dobutamine and dopexamine. The clinical relevance of such effects requires further investigation in critically ill patients. (*Br. J. Anaesth.* 1997; **78**: 530–535).

Key words
Blood, leucocytes. Blood, lymphocytes. Blood, neutrophils. Sympathetic nervous system, catecholamines.

There is increasing evidence to suggest that the neuroendocrine system interacts with, and is a potent modulator of, the immune system. Endogenous catecholamine release caused by stress induces leucocytosis.[1–3] Exercise increases both lymphocyte and neutrophil numbers,[2 4] but major surgical stress causes lymphopenia with polymorphonuclear leucocytosis.[1 5] Furthermore, increased release of cortisol accompanying stress, such as in major surgery, also affects leucocyte numbers.[6 7] Exogenous administration of adrenaline also induces leucocytosis with an initial increase in lymphocytes followed by neutrophilia and relative lymphopenia.[7–9]

Lymphocytes can be divided further into several subsets which include B lymphocytes, T lymphocytes and natural killer (NK) cells. Exercise-induced increases in adrenaline result in lymphocytosis, with a three-fold increase in cytotoxic T cells (CD8$^+$) and NK cells, and a smaller increase in helper T cells (CD4$^+$).[10 11] Exogenous administration of adrenaline alters the subtypes of lymphocytes: an increase in NK cells has been found consistently,[6 7 12 13] but although Brohee and colleagues[7] showed an increase in all lymphocytic subtypes, others have found that total T cell (CD3$^+$) and CD4$^+$ counts decreased.[6 12 13] This effect is thought to be caused by stimulation of β_2-adrenergic receptors on lymphocytes.[10 14 15] Prolonged exposure to catecholamines can lead to a reduction in the number of circulating lymphocytes in healthy volunteers.[16]

Catecholamines also affect white cell function. Administration of adrenaline has been shown to decrease neutrophil adherence *in vitro*,[13 17] decrease chemotaxis[18] and enhance NK activity.[6 12 19] Such changes in the immune system may be clinically important after major surgery, trauma and in the critically ill patient with sepsis.

The majority of studies in this field have been performed with adrenaline as the primary stimulant. Adrenaline stimulates α_1-, β_1- and β_2-adrenergic receptors. In contrast, the synthetic inotropic agents dobutamine and dopexamine have no α_1 agonist

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activity. Dobutamine is a β_1- and β_2-adrenoceptor agonist,[20] while dopexamine stimulates dopaminergic and β_2- adrenoceptors, with minimal β_1-receptor activity.[21] Park, Couzens and Hoskins found that total white cell count increased during infusion of dopamine, dobutamine or dopexamine,[22] but little is known of the effects of these synthetic inotropic agents on white cell populations and function. The complexity of the interactions between the immune system and the neuroendocrine system make it unwise to extrapolate from studies with adrenaline to newer inotropic agents with different adrenergic receptor specificity. In view of the large number of immune variables thought to be affected by these agents, we chose to perform a pilot study. The aim of this study was to investigate the effects of inotropes with different adrenoceptor specificity on differential white cell count, lymphocyte subtypes and neutrophil function in six healthy volunteers.

Subjects and methods

This pilot study was a placebo-controlled study of the effects of adrenaline, dobutamine and dopexamine on white cell count, lymphocyte subtype count and neutrophil function in healthy volunteers. Volunteers were studied on four different occasions, each at least 1 week apart. All studies started between 08:00 and 09:30 to avoid confounding effects of circadian rhythms on the variables measured. Each volunteer was allocated randomly to receive the different agents in a different order. Volunteers and laboratory investigators, but not the clinical investigator, were blinded to the drug administered. Approval from the local District Ethics Committee was obtained.

We studied six healthy male volunteers. Before recruitment, any volunteer with a history of chronic illness, receiving treatment for intercurrent illness, a history of drug or alcohol (>25 units/week) abuse or cigarette smoking, or known allergy to inotropic agents was excluded. Written informed consent was obtained from each volunteer and a full physical examination with laboratory and electrocardiographic assessment was performed by an independent physician, before and at the end of the study.

INOTROPE ADMINISTRATION

The study was conducted in an area which had full resuscitation facilities and a physician in attendance at all times. A 16-gauge cannula was inserted into each forearm under local anaesthesia: one cannula was used for blood sampling and the other for administration of the test substance only. Haemodynamic monitoring with continuous ECG and an automatic intermittent arterial pressure monitoring device was then started. After a baseline reading, arterial pressure was measured at 2 and 5 min after starting the infusion, and then at 5-min intervals throughout the infusion and the 30-min period after the infusion was stopped. Additional readings were obtained at 3 and 4 h after starting the study. Volunteers remained recumbent throughout the study. Coffee or tea was avoided for 8 h before the study, and only orange squash, toast and biscuits were allowed throughout the study.

Volunteers were studied during a 2-h infusion, and for 2 h after completion of the study. The agents investigated were adrenaline 0.1 μg kg^{-1} min^{-1}, dobutamine 5 μg kg^{-1} min^{-1}, dopexamine 2 μg kg^{-1} min^{-1} and 5% glucose 0.5 ml kg^{-1} h^{-1} as placebo. The infusion rate was halved or stopped if heart rate exceeded 120 beat min^{-1}, arrhythmia developed or mean arterial pressure changed by more than 20 mm Hg.

Venous blood was sampled before starting the infusion ($t=0$), at 30 and 120 min after starting the infusion, and 2 h after stopping the infusion. A maximum of 30 ml of blood were required at each sampling time: 20 ml of heparinized blood for neutrophil studies, 2 × 2.7 ml in EDTA for differential white cell count and lymphocyte subtypes, and 5 ml of spare serum in the event of further tests being required to validate results. Differential white count and lymphocyte subtypes were measured at all four times, and neutrophil function was measured at 0, 30 and 120 min.

MEASUREMENT OF HAEMATOLOGICAL AND IMMUNOLOGICAL VARIABLES

A full blood count and white cell differential count were performed using a STK-S Coulter counter (Coulter Electronics, UK). Where an automated white cell differential count could not be obtained, a manual white cell differential was performed.

Lymphocyte subtypes were assessed by dual colour immunofluorescence using a lysed whole blood technique. The markers used were CD19$^+$ (B cells), CD3$^+$ (total T cells), CD4$^+$ (T helper cells), CD8$^+$ (cytotoxic T cells), CD3$^+$/DR co-expression (activated T cells) and CD16$^+$ (NK cells). All reagents were from the Simulset range of monoclonal antibodies (Becton Dickinson, Oxford, UK). The percentage of each T cell subtype was measured by flow cytometry using a FACScan (Becton Dickinson, Oxford, UK) and Simulset software. Absolute values were calculated from this percentage and lymphocyte count from full blood count.

Blood for neutrophil function assays was obtained under pyrogen-free conditions into preservative-free heparin. All assays of neutrophil function were carried out under pyrogen-free conditions. The assays used do not require highly purified neutrophil populations, and so gravity sedimented leucocytes were used to avoid unnecessary manipulation of neutrophils.

Neutrophil respiratory burst in response to formyl-methionyl-leucyl-phenylalanine (fMLP) (Sigma, UK) was assessed using a luminiol-enhanced chemoluminescence system. Phagocytosis of both opsonized and unopsonized zymosan was assessed indirectly, using a luminol-enhanced chemoluminescence system. The chemotactic response (directional movement of neutrophils towards a stimulus with chemoattractant properties) together with chemokinesis (non-directional, random neutrophil motility) was assessed under agarose.[23] The chemotactic responses to different stimuli (fMLP, autologous serum, zymosan-activated serum and normal pooled human serum) were tested. Neutrophil adhesion to protein-coated glass was assessed by microscopy in a chamber assay.[24] The expression of CD11b, a component of the CD11b/CD18 integrin adhesion molecule, was measured by flow cytometry.

STATISTICAL ANALYSIS

As all of the immunological variables measured vary greatly both within- and between-individuals, changes during each study were expressed as percentage change from baseline (measurement at $t=0$). Results are expressed as mean (SEM) percentage change from baseline where $n=6$. The Wilcoxon signed rank test was used to compare differences between placebo and active drugs on changes from baseline at each time.

Results

All six volunteers completed the four study periods. The infusion rate was halved only once, when mean arterial pressure decreased by greater than 20%, 5 min after an infusion of adrenaline was started. Arterial pressure then returned to baseline values. On all other occasions heart rate and mean arterial pressure remained within the predetermined limits. No arrhythmias occurred. Volunteers noted a variety of subjective sensations, including tremor, headache and awareness of the heart beating, but they were not distressed by these symptoms.

Data for all variables were obtained, except in the following instances: monocyte and basophil counts were not obtained for one study because of a technical problem with the Coulter counter, and platelet count was not obtained for all four studies in one volunteer because of platelet clumping. This is a problem which can occur in normal individuals and did not signify any significant underlying disease.

HAEMATOLOGICAL VARIABLES

Mean percentage changes from baseline for differential white cell count and lymphocyte subtypes that occurred during infusion of each of the four agents at each time, and the significance of these changes compared with placebo, are shown in tables 1 and 2, respectively. Infusion of adrenaline was associated with significant leucocytosis, lymphocytosis and neutrophilia, whereas infusions of dobutamine and dopexamine were associated with a significant decrease in white cell, lymphocyte and neutrophil counts. These changes were also apparent for absolute CD3$^+$ count (total T cells), absolute CD4$^+$ count (helper T cells) and absolute CD8$^+$ count (cytotoxic T cells). Monocytes increased significantly only during infusion of adrenaline, whereas eosinophil count increased initially with infusion of adrenaline, and then decreased with infusion of all three agents. There were no significant changes in haemoglobin, packed cell volume or red cell count. Platelet count increased significantly with infusion of adrenaline compared with placebo at 30 ($P=0.043$) and 120 min ($P=0.043$).

NEUTROPHIL FUNCTION

Mean percentage changes from baseline for the neutrophil function tests that occurred with infusion of each of the four agents at each time, and the significance of these changes compared with placebo, are shown in table 3. There was a significant increase in chemoluminescence with infusion of adrenaline for 30 min compared with placebo ($P=0.046$). Neutrophil adhesion, CD 11b expression and phagocytosis were not changed significantly by infusion of any of the test drugs at the given dose. Chemotaxis (directional neutrophil movement) to fMLP, the volunteer's own serum, normal human serum and zymosan-activated serum did not change significantly. Chemokinesis (non-directional random

Table 1 Mean (SEM) percentage changes from baseline in differential white cell count at 30, 120 and 240 min after starting the four infusions ($n=6$). *$P<0.05$ (Wilcoxon signed rank test)

	Total white cell count			Lymphocyte count			Neutrophil count		
Time (min)	30	120	240	30	120	240	30	120	240
Glucose	−1.67 (4.4)	+6.92 (4.7)	+10.5 (5.1)	−2.8 (8.2)	+5.8 (11.9)	+13.7 (6.4)	−0.13 (3.2)	+10.3 (5.4)	+7.67 (12.6)
Adrenaline	+70.5 (12.8)*	+60.1 (13.4)*	+91.8* (29.2)*	+126 (28.7)*	+37.1 (12.2)*	−5.0 (6.6)*	+33.6 (6.2)*	+82.0 (21.7)*	+160 (48.2)*
Dobutamine	−8.3 (2.0)	−11.2 (2.8)*	−1.7 (2.9)	−6.4 (3.4)	−16.2 (6.8)*	−4.2 (3.6)	−9.8 (2.0)*	−8.2 (4.1)*	−3.1 (3.9)
Dopexamine	−6.3 (2.3)	−13.5 (2.6)*	+1.5 (5.6)	+14.4 (10.5)*	−11.9 (8.2)*	−16.1 (7.8)*	−15.1 (1.8)*	−11.2 (3.4)*	+11.4 (12.9)

	Monocyte count			Basophil count			Eosinophil count		
Time (min)	30	120	240	30	120	240	30	120	240
Glucose	−4.7 (4.4)	−13.0 (6.8)	+1.8 (8.3)	+12.5 (20.4)	0 (16.1)	+147.5 (153)	−8.1 (4.2)	+4.4 (7.7)	+5.0 (2.7)
Adrenaline	+81.6 (19.2)*	+56.8 (11.2)*	+106 (49.5)	+38.5 (37.1)	−61.5 (21.6)	−46.2 (38.2)	+54.9 (12.1)*	−18.1 (8.1)	−51.9 (6.5)*
Dobutamine	−12.9 (6.8)	−15.2 (5.1)	−6.8 (5.0)	−39.3 (15.3)	−10.7 (53.7)	71.4 (185)	−17.9 (5.9)	−29.3 (2.8)*	−28.6 (7.6)*
Dopexamine	−21.0 (5.6)	−21.0 (7.0)	+3.6 (15.4)	+44.4 (56.2)	−27.8 (14.2)	350 (196)	−42.6 (7.4)*	−54.1 (3.9)*	−61.5 (4.5)*

Table 2 Mean (SEM) percentage changes from baseline in lymphocyte subsets at 30, 120 and 240 min after starting the four infusions ($n = 6$). *$P < 0.05$ (Wilcoxon signed rank test)

	CD19 absolute count (B cells)			CD3 absolute count (total T cells)			ACT absolute count (activated T cells)		
Time (min)	30	120	240	30	120	240	30	120	240
Glucose	+1.5 (9.9)	+13.2 (14.8)	+11.2 (13.1)	−2.1 (7.2)	+7.7 (10.8)	+14.9 (7.1)	−5.6 (5.5)	+23.1 (16.9)	+36.1 (13.7)
Adrenaline	+50.3 (49.9)	+16.0 (9.4)	+15.4 (21.5)	+96.5 (19.8)*	+23.3 (10.6)	−10.6 (7.9)	+263 (135)*	+70.8 (24.3)	−29.2 (13.7)
Dobutamine	−20.0 (4.2)	−6.1 (9.4)	+9.4 (6.0)	−13.1 (3.2)*	−19.0 (7.5)*	−5.2 (5.2)	+13.9 (14.8)	−11.8 (11.2)	−21.6 (5.7)*
Dopexamine	−22.1 (5.0)	−23.6 (5.6)	−18.1 (14.7)	+1.1 (8.9)	−19.1 (7.0)*	−15.9 (9.2)	+20.6 (9.0)	–21.6 (12.4)	−28.4 (15.3)*

	CD4 absolute count (T helper cells)			CD8 absolute count (T suppressor cells)			NK absolute count (natural killer cells)		
Time (min)	30	120	240	30	120	240	30	120	240
Glucose	−3.6 (6.8)	+7.1 (10.1)	+15.2 (5.8)	−3.1 (9.3)	+9.4 (15.4)	+19.7 (8.6)	0 (22.9)	+32 (35.3)	+74 (35.1)
Adrenaline	+69.9 (22.4)*	+1.5 (10.4)	0 (7.1)	+213 (32.3)*	+53 (20.3)	+130 (136)*	+739 (345)*	+340 (106)	+1.3 (17.1)*
Dobutamine	−12.5 (2.2)	−17.6 (6.7)*	+2.7 (4.1)	+15.0 (7.3)	−9.8 (7.5)	−6.8 (4.5)*	+69 (36.6)	–6.3 (12.5)	−25 (12.9)*
Dopexamine	−29.9 (13.8)	−19.1 (5.7)*	−8.2 (10.2)	+40.0 (17.9)*	−5.6 (11.6)	−31.0 (5.4)*	+216 (80.9)*	+75 (42.0)	+35 (50.8)

Table 3 Mean (SEM) percentage changes from baseline in neutrophil function tests at 30 and 120 min after starting the four infusions ($n = 6$). *$P < 0.05$ (Wilcoxon signed rank test)

	Chemoluminescence		Phagocytosis (opsonized zymosan)		Adhesion		Chemotaxis to fLMP	
Time (min)	30	120	30	120	30	120	30	120
Glucose	+3.0 (36.8)	−9.1 (26.4)	−19.2 (15.3)	−0.8 (25.7)	−20.1 (15.7)	−26.2 (8.5)	+18.5 (18.7)	+13.9 (13.9)
Adrenaline	+55.8 (19.4)*	+23.8 (20.5)	+12.9 (25.0)	+29.0 (19.3)	+1.3 (16.9)	−16.1 (13.5)	+27.2 (19.9)	+17.7 (12.4)
Dobutamine	−20.7 (439)	−27.8 (180)	+14.7 (29.2)	+6.4 (32.8)	−32.3 (6.9)	−19.4 (8.2)	+18.0 (15.7)	+11.3 (10.4)
Dopexamine	+32.1 (65.1)	+16.5 (64.6)	−29.8 (16.9)	+13.7 (41.3)	−31.9 (7.7)	−34.1 (12.4)	−4.2 (10.5)	−5.2 (2.4)

	Chemotaxis to autologous serum		Chemotaxis to zymosan activated serum		Chemotaxis to normal pooled serum		Chemokinesis	
Time (min)	30	120	30	120	30	120	30	120
Dextrose	+7.0 (33.6)	+19.9 (16.0)	+32.3 (41.9)	+12.1 (17.9)	−0.2 (35.8)	+18.3 (16.1)	−8.3 (12.6)	+5.8 (15.8)
Adrenaline	+59.9 (26.6)	+38.0 (20.1)	+28.6 (14.6)	+37.1 (26.2)	+23.2 (12.8)	+29.6 (32.1)	−20.0 (12.4)	−12.9 (23.3)
Dobutamine	+36.3 (23.3)	+51.3 (26.4)	+72.7 (23.7)	+54.9 (15.7)	+62.5 (37.3)	+72.6 (29.8)	+35.1 (26.8)*	+48.9 (19.6)
Dopexamine	−7.2 (15.0)	+71.8 (24.1)	−10.4 (23.0)	+61.3 (52.6)	−21.2 (8.6)	+45.0 (37.3)	+12.9 (16.8)	+70.5 (22.2)

movement) increased significantly 30 min after infusion of dobutamine compared with placebo ($P = 0.03$). However, as chemotaxis was unaffected, this effect is unlikely to be clinically relevant.

Discussion

We found a significant increase in white cell count, lymphocyte count and neutrophil count with adrenaline, and a small but significant decrease in these variables with dobutamine and dopexamine.

These trends were also apparent for absolute CD3^{+}, CD4^{+} and CD8^{+} counts. Chemoluminescence increased significantly only with adrenaline, and there were no other significant changes in tests of neutrophil function.

Leucocytosis, lymphocytosis and neutrophilia in association with exogenous administration of adrenaline is well recognized. Changes in circulating leucocyte numbers may be caused by an absolute change in total leucocyte count or alteration in the fraction of leucocytes present in the circulation. Two populations of neutrophils have been identified: circulating and marginal. Adrenaline appears to mobilize the marginating pool into the circulating pool without altering the total neutrophil population.[25] After major surgical stress lymphopenia is associated with redistribution of lymphocytes from the blood to lymphatic tissue.[26] Of interest was the significant decrease in white cell numbers, lymphocyte and neutrophil counts which was evident during infusion of the synthetic agents dobutamine and dopexamine. These trends were also apparent for absolute $CD3^+$ count (total T cells), absolute $CD4^+$ count (helper T cells) and absolute $CD8^+$ count (cytotoxic T cells). All three agents increased natural killer cell count, as has been described previously with adrenaline. These changes are of interest, but are difficult to interpret in a clinical setting as they probably reflect transient changes in the intravascular pool which may not reflect events in the tissues. Our results are in contrast with the increase in white cell count seen with infusion of dobutamine or dopexamine in the study by Park, Couzens and Hoskins,[22] which may reflect the higher doses of these agents used in their study. The differences between adrenaline and the synthetic inotropes may reflect the different β_2-adrenergic activity of the agents, despite the doses being chosen with a view to equipotency. However, each volunteer has a different pharmacodynamic response to each agent, depending on factors such as the concentration of endogenous circulating catecholamines, and variation between individuals for a given dose may account in part for the differences seen.

The numbers of monocytes increased only during infusion of adrenaline, whereas eosinophil count increased initially with infusion of adrenaline, and then decreased with infusion of all three agents. These changes probably reflect changes in the white cell populations between circulating and marginal pools. A significant increase in platelet count was seen only with adrenaline. Adrenergic stimulation increases platelet numbers and activation, while β_2-adrenergic stimulation decreases platelet numbers and platelet aggregation.[27 28] The effect of adrenaline was caused presumably by α-adrenergic stimulation; neither dobutamine nor dopexamine possess α-agonist activity. It is important that clinicians recognize such effects when interpreting laboratory data from patients receiving these agents, as this may avoid unnecessary investigation of drug-related changes.

The effect of infusion of adrenaline on chemoluminescence is of interest, suggesting an increase in the generation of reactive oxygen species by the neutrophil. However, another possible explanation is that the marginating neutrophil pool mobilized by adrenaline may be of a functionally more active group of neutrophils. The role of neutrophil activation resulting in increased free radical production and direct tissue damage in the pathophysiology of multiple organ failure and acute lung injury is well recognized.[29 30] In view of the widespread use of inotropes, the relevance of neutrophil activation in patients would certainly be worthy of further study. As adrenaline, dobutamine and dopexamine infusions had no effect on neutrophil chemotaxis, it is unlikely that the acute effect of dobutamine on chemokinesis is clinically important.

This preliminary study was designed to identify specific variables which could then be studied on a larger scale in both volunteers and specific patient populations. The problems associated with determining a normal range for lymphocyte subsets and neutrophil function are reduced by using volunteers as their own controls. While a small study in which so many variables are measured is likely to show some statistically significant results, further work is required to determine which of these results is clinically important.

In summary, this study suggests that infusion of inotropes was associated with changes in white cell numbers, lymphocyte subsets and neutrophil respiratory burst. Adrenaline had effects different from those of the synthetic inotropic agents, dobutamine and dopexamine, at least in healthy volunteers. The study highlighted areas in which further work is needed to determine the clinical relevance of immunological effects of different inotropic agents.

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